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## CLINICAL RESEARCH

# Absence of additional improvement in outcome of patients receiving cardiac resynchronization therapy paced at the most delayed left ventricular region

Stimuler la paroi ventriculaire gauche la plus retardée ne permet pas de bénéfice supplémentaire chez les patients resynchronisés

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### KEYWORDS

Cardiac resynchronization therapy;  
Left ventricular pacing site;  
Echocardiography

### Summary

**Background.** — The choice of the optimal left ventricular (LV) pacing site remains an issue in patients requiring cardiac resynchronization therapy (CRT).

**Aim.** — This prospective study compared the outcome of patients paced at the most delayed LV region with that of patients paced at any other LV site.

**Methods.** — Forty-four patients with severe heart failure underwent three-dimensional (3D) echocardiography before implantation and 3 days after implantation of a CRT device, to determine the most delayed LV region during spontaneous rhythm and during right ventricular pacing. The patients were divided subsequently into four groups: group 1 ( $n=19$ ), LV lead placed at the most delayed echocardiographic site in spontaneous rhythm; group 2 ( $n=25$ ), LV lead placed at any other site; group 3 ( $n=21$ ), LV lead placed at the most delayed echocardiographic site during right ventricular pacing; group 4 ( $n=23$ ), LV lead placed at any other site.

**Results.** — No significant differences were observed between the four groups before implantation. After 6 months of CRT, no significant differences were observed between groups 1 and 2 or between groups 3 and 4 in terms of change in New York Heart Association functional class, Minnesota living with heart failure questionnaire, 6-minute walk test, peak exercise oxygen consumption, 3D ventricular dyssynchrony and 3D LV ejection fraction.

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## MOTS CLÉS

Resynchronisation  
biventriculaire ;  
Site de stimulation  
ventriculaire gauche ;  
Échocardiographie

**Conclusion.** — Implantation of the LV lead in the most delayed region of the left ventricle determined by 3D echocardiography did not result in additional improvement in symptoms or LV function.

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## Résumé

**Introduction.** — Chez les patients bénéficiant d'une resynchronisation biventriculaire, le choix du site optimal de stimulation ventriculaire gauche reste controversé. Cette étude prospective compare le devenir de patients stimulés au niveau de la région ventriculaire gauche (VG) la plus retardée et le devenir de patients stimulés dans une autre région.

**Méthode.** — Quarante-quatre patients insuffisants cardiaques bénéficièrent d'une échocardiographie tridimensionnelle (3D) avant l'implantation et trois jours après pour déterminer la paroi la plus retardée en rythme spontané (RS) et lors d'une stimulation ventriculaire droite (VD). Les patients étaient divisés en quatre groupes : groupe 1 ( $n = 19$ ) : sonde VG placée au niveau de la paroi la plus retardée en RS ; groupe 2 ( $n = 25$ ) : sonde VG placée sur une autre paroi ; groupe 3 ( $n = 21$ ) : sonde VG placée au niveau de la paroi la plus retardée lors d'une stimulation VD ; groupe 4 ( $n = 23$ ) : sonde VG placée sur une autre paroi.

**Résultats.** — Nous n'avons pas retrouvé de différence significative entre les quatre groupes avant l'implantation. Après six mois de stimulation, nous n'avons pas retrouvé de différence significative entre les patients des groupes 1 et 2 et des patients des groupes 3 et 4 en termes de modification de classe *New York Heart Association*, de questionnaire de qualité de vie, de périmètre de marche, de pic de  $VO_2$ , d'asynchronisme 3D et de fraction d'éjection.

**Conclusion.** — L'implantation de la sonde ventriculaire gauche dans la paroi la plus retardée n'a pas permis d'apporter un bénéfice supplémentaire en termes de symptômes et de fonction ventriculaire gauche.

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## Abbreviations

3D	three-dimensional
CRT	cardiac resynchronization therapy
LV	left ventricular
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume

## Introduction

CRT has an established role in the management of patients with advanced heart failure and prolonged QRS duration [1–3]. However, one third of patients do not respond to CRT, despite the application of established electrocardiographic selection criteria [4]. To improve outcome and reduce the proportion of non-responders, three different and complementary approaches have been proposed: optimization of patient selection; optimization of LV lead placement and optimization of the programming of the CRT device [5–10]. To date, identification of the optimal LV lead position has attracted little attention. Previous studies have suggested that implantation of the LV lead in the area of the most delayed pre-implantation echocardiographically-determined electromechanical activation may be associated with an improvement in the response to CRT and a decrease in the proportion of non-responders [11–13]. Similarly, placement of the LV electrode in the area with maximal delay during right ventricular pacing may optimize the electromechanical activation. The aim of the present study was

to evaluate, by use of 3D echocardiography, the putative favourable impact on the efficacy of CRT, in terms of ventricular dyssynchrony and midterm clinical status, of an echocardiographically-optimized LV lead position targeting the exact region of maximal mechanical delay during spontaneous rhythm and during right ventricular pacing.

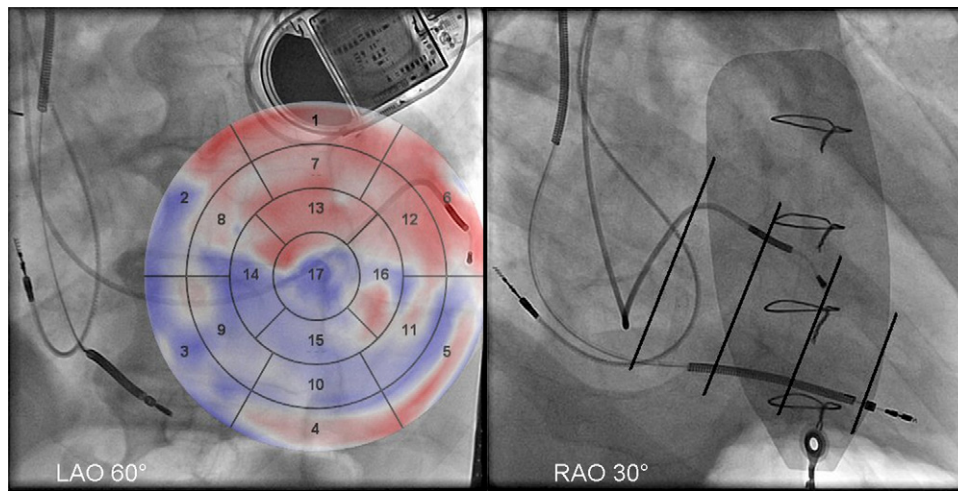
## Methods

### Study population

Forty-four successive patients with refractory heart failure due to severe systolic dysfunction, prolonged QRS duration, in sinus rhythm and scheduled for implantation of a CRT device were enrolled prospectively. Refractory heart failure was defined by the persistence of New York Heart Association functional class III or IV despite optimal pharmacological therapy. Severe systolic dysfunction was defined by a LVEF less than 35%, while prolonged QRS duration was defined by a QRS width greater than 120 ms. Patients were excluded from the study if they had a history of sustained atrial arrhythmias or complete atrioventricular block or a poor ultrasonic window that did not allow exploitable 3D acquisitions. All patients provided written, informed consent to the study, which was approved by the institutional clinical research and ethics committee.

### Study protocol

All patients underwent echocardiography, a quality-of-life assessment using the Minnesota living with heart failure



**Figure 1.** After implantation of the cardiac resynchronization therapy device, fluoroscopic orthogonal views (right anterior oblique [RAO] at 30° and left anterior oblique [LAO] at 60°) were acquired. LAO at 60°: the resized 16-segment scheme was projected. RAO: divided into basal, medial and apical sections.

questionnaire, a 6-minute hall walk test and a maximal bicycle and treadmill cardiopulmonary test with measurement of peak exercise oxygen consumption within 5 days before implantation and after 6 months of simultaneous biventricular pacing.

#### Biventricular device implantation and programming

All leads were implanted transvenously. The atrial lead was positioned conventionally at the right atrial appendage and the right ventricular lead at the apex of the right ventricle. The LV lead was positioned through the coronary sinus into a posterior ( $n=9$ ), lateral ( $n=23$ ) or anterior ( $n=12$ ) cardiac vein. The physician who implanted the LV lead was blinded to the results of the echocardiographic examination. In clinical practice, a lateral or a posterior vein is usually targeted. In this study, the priority was to achieve a stable position with suitable threshold and absence of diaphragmatic pacing. No intraoperative haemodynamic evaluation was carried out. The pacing leads were connected to a biventricular implantable cardioverter-defibrillator (InSync Sentry 7298, Medtronic [Minnesota, USA] Contak Renewal 4 HE, Guidant [Minneapolis, USA]). For 3 days, the patients were not paced in the ventricles (AAI mode, 40 beats/minute). Three days after implantation, the atrioventricular delay was optimized echocardiographically during biventricular pacing to provide the longest transmitral LV filling time without truncation of the A-wave obtained from pulsed Doppler analysis of the LV filling. The interventricular timing was set to 0 in all patients.

#### Echocardiographic evaluations

Real-time 3D echocardiography was performed 3 days before implantation, 3 days after implantation and after 6 months of simultaneous biventricular pacing, using a 3D probe connected to a 3D digital ultrasound system (Vivid 7, GE Vingmed, Horton, Norway). During the echocardiography 3 days after implantation, echocardiographic recordings were made during atrio-sensed right ventricular pacing and

atrio-sensed simultaneous biventricular pacing. All echocardiographic recordings were made by the same physician to minimize variability between examinations. All images were recorded digitally and analysed off-line. The off-line analysis was performed by an observer blinded to the fluoroscopic lead positions (Fig. 1). A full-volume loop of the left ventricle was acquired using an apical position of the probe during a short breath hold. The LVEF, LVESV and LVEDV were determined off-line with the aid of semiautomatic contour tracing software (4D LV-Analysis, TomTec, Unterschleissheim, Germany) as described previously [14]. A 3D parameter of dyssynchrony was obtained from the time-course of shortening in 16 LV segments and the resulting segmental volume/time curves. The 3D dyssynchrony index was defined as the standard deviation of the 16 segmental shortening durations to reach minimum segmental volume [15]. To allow comparisons between patients with significantly different heart rates, this variable was expressed as a percentage of the cardiac cycle duration.

Based on the resulting segmental volume/time curve in each patient, the segment with the latest minimum of systolic volume as an indicator for latest systolic contraction was identified before implantation and defined as the segment with maximum mechanical delay. Similarly, 3 days after implantation, the segment with the latest minimum of systolic volume as an indicator for latest systolic contraction was identified during right ventricular pacing.

#### Concordance between most delayed echocardiographic left ventricular segment (spontaneous rhythm and right ventricular pacing) and left ventricular pacing site

After CRT implantation, biplane fluoroscopy was performed in left anterior and right anterior oblique orthogonal views. These images were analysed by two independent physicians using a 16-segment scheme, identical to the scheme used in the 4D LV-analysis (TomTec, Unterschleissheim, Germany)

and projected onto the left anterior oblique view to determine the anatomical location of the LV lead within the circumference of that level. The right anterior oblique view was used subsequently to define the basal, medial or apical level of the LV lead.

A correlation between the fluoroscopic LV pacing site and the most delayed echocardiographically-determined LV site was assessed blindly, as described previously [11], by two observers with full concordance. The physicians performing echocardiographic analysis and classification of LV lead position as optimal or non-optimal were blinded with regard to possible difficulties during LV lead placement and anatomical limitations.

## Statistical analysis

Interobserver and intraobserver reproducibility of 3D echocardiographic measurements were assessed with linear regression analysis and the Bland-Altman method in 32 patients (mean age  $53 \pm 16$  years; 28 men) who were not included in the present study. These patients were selected to demonstrate different levels of LV dysfunction ranging from normal heart to severe cardiomyopathy. Continuous variables are presented as means  $\pm$  standard deviations. Categorical data are presented as frequencies and percentages. Sequential data measurements were analysed by repeated measures analysis of variance followed by Scheffé's procedure for multiple comparisons. Statistical significance was established at  $p < 0.05$ .

## Results

The patients' baseline characteristics are presented in Table 1. The entire study protocol was completed in all 44 patients. No patient died during the 6-month follow-up period. Interobserver variability mean average error and 95% confidence interval values obtained from the Bland and Alt-

man analysis of 3D LVEF, 3D LVESV and 3D LVEDV were  $-0.2$  and  $3.3\%$ ,  $-1.2$  and  $13.7$  mL, and  $-0.2$  and  $16.1$  mL, respectively. Intraobserver variability mean average error and 95% confidence interval values obtained from the Bland and Altman analysis of 3D LVEF, 3D LVESV and 3D LVEDV were  $0.1$  and  $2.8\%$ ,  $-0.1$  and  $8.4$  mL, and  $0.3$  and  $9.6$  mL, respectively (Figs. 2 and 3).

In 19 patients (Group 1), the LV lead position determined by fluoroscopy was found to be concordant with the site of the most delayed mechanical activation determined in spontaneous rhythm before implantation. The LV lead was positioned in the following segments: nine lateral (three basal, five medial and one apical), six anterior (two basal and four medial) and four posterior (one basal and three medial). In 25 patients (Group 2), the LV lead position did not match with the most delayed site. The LV lead was positioned in the following segments: 14 lateral (four basal, nine medial and one apical), six anterior (four basal and two medial) and five posterior (four medial and one apical).

In 21 patients (Group 3), the LV lead position determined by fluoroscopy was found to be concordant with the site of the most delayed mechanical activation determined during right ventricular pacing after implantation. The LV lead was positioned in the following segments: 11 lateral (five basal, five medial and one apical), four anterior (three basal and one medial) and six posterior (one basal and five medial). In 23 patients (Group 4), the LV lead position did not match with the most delayed site during right ventricular pacing. The LV lead was positioned in the following segments: 12 lateral (two basal, nine medial and one apical), eight anterior (three basal and five medial) and three posterior (two medial and one apical).

There was no difference between patients in Groups 1 and 2 or between patients in Groups 3 and 4 in terms of demographic, clinical and echocardiographic characteristics at baseline, or in the distribution of the location of the most delayed segment (Tables 2 and 3).

Three days after implantation, a significant increase was observed compared with baseline in real-time 3D echocardiographically-determined LVEF ( $31.8 \pm 7\%$  vs  $25.8 \pm 7\%$ ,  $r < 0.05$ ) and a decrease in the dyssynchrony index ( $6.7 \pm 1.8\%$  vs  $9.9 \pm 2.9\%$ ;  $p < 0.05$ ) in the overall population, without significant difference between the four groups.

After 6 months of simultaneous biventricular pacing, a significant improvement was observed in clinical status in terms of New York Heart Association functional class ( $2.3 \pm 0.3$  vs  $3.2 \pm 0.3$ ,  $p < 0.05$ ), Minnesota living with heart failure questionnaire ( $30 \pm 15$  vs  $54 \pm 18$ ,  $p < 0.05$ ), 6-minute walk test ( $415 \pm 83$  m vs  $296 \pm 69$  m,  $p < 0.05$ ) and peak oxygen consumption ( $15.2 \pm 3.8$  mL/kg/min vs  $13.4 \pm 3.5$  mL/kg/min,  $p < 0.05$ ) in the overall population, compared with baseline. These beneficial effects of CRT were supported by a decrease in LVESV ( $99 \pm 48$  mL vs  $130 \pm 69$  mL,  $p < 0.05$ ) and LVEDV ( $144 \pm 60$  mL vs  $176 \pm 80$  mL,  $p < 0.05$ ), an increase in LVEF ( $33.3 \pm 6.4\%$  vs  $27.5 \pm 7\%$ ,  $p < 0.05$ ) and a decrease in the dyssynchrony index ( $4.9 \pm 1.2\%$  vs  $9.9 \pm 2.9\%$ ,  $p < 0.05$ ).

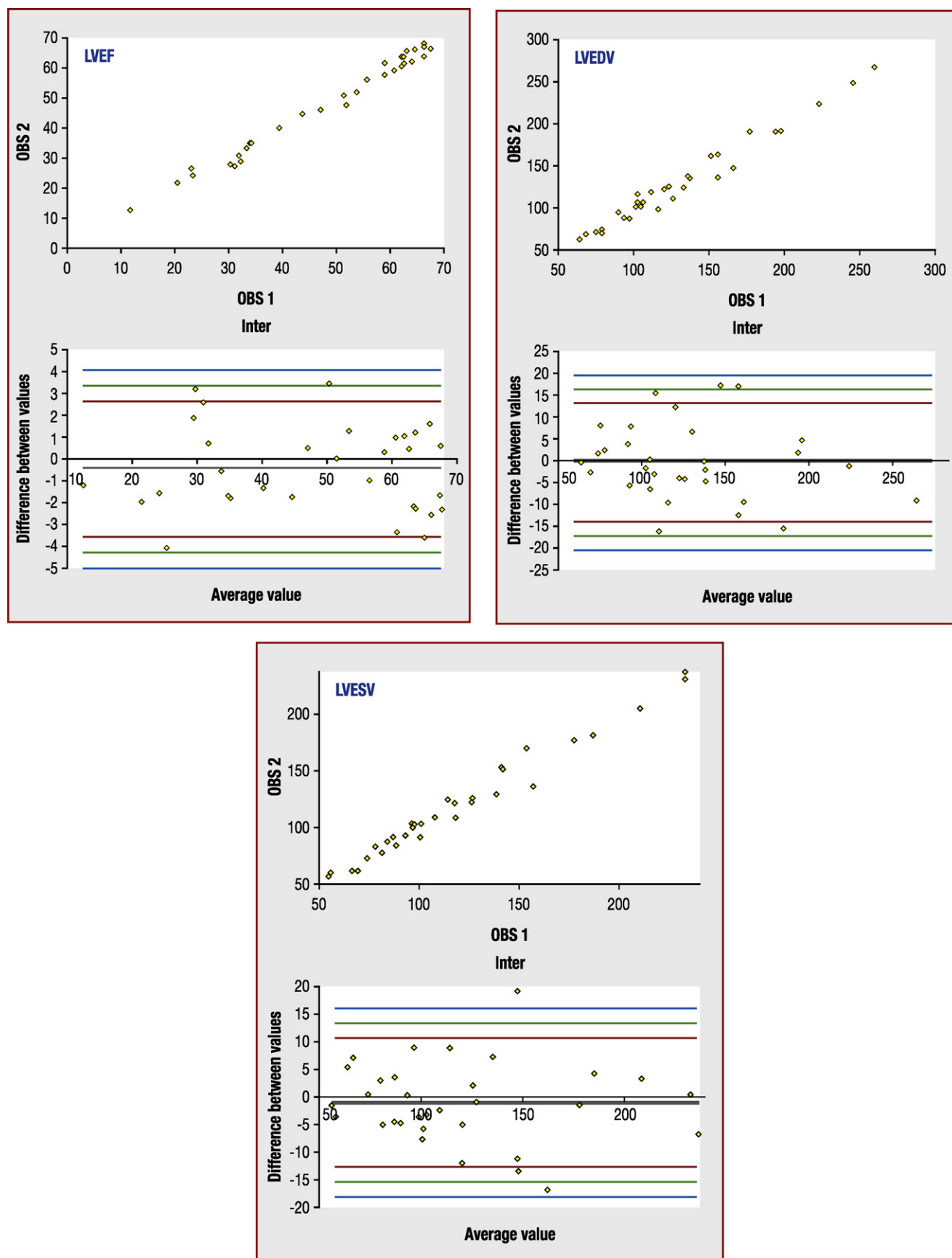
After 6 months of simultaneous biventricular pacing, no significant differences were observed in any of the studied variables between patients in Group 1 and Group 2 or between patients in Group 3 and Group 4.

**Table 1** Demographic and clinical characteristics at baseline; total population ( $n = 44$ ).

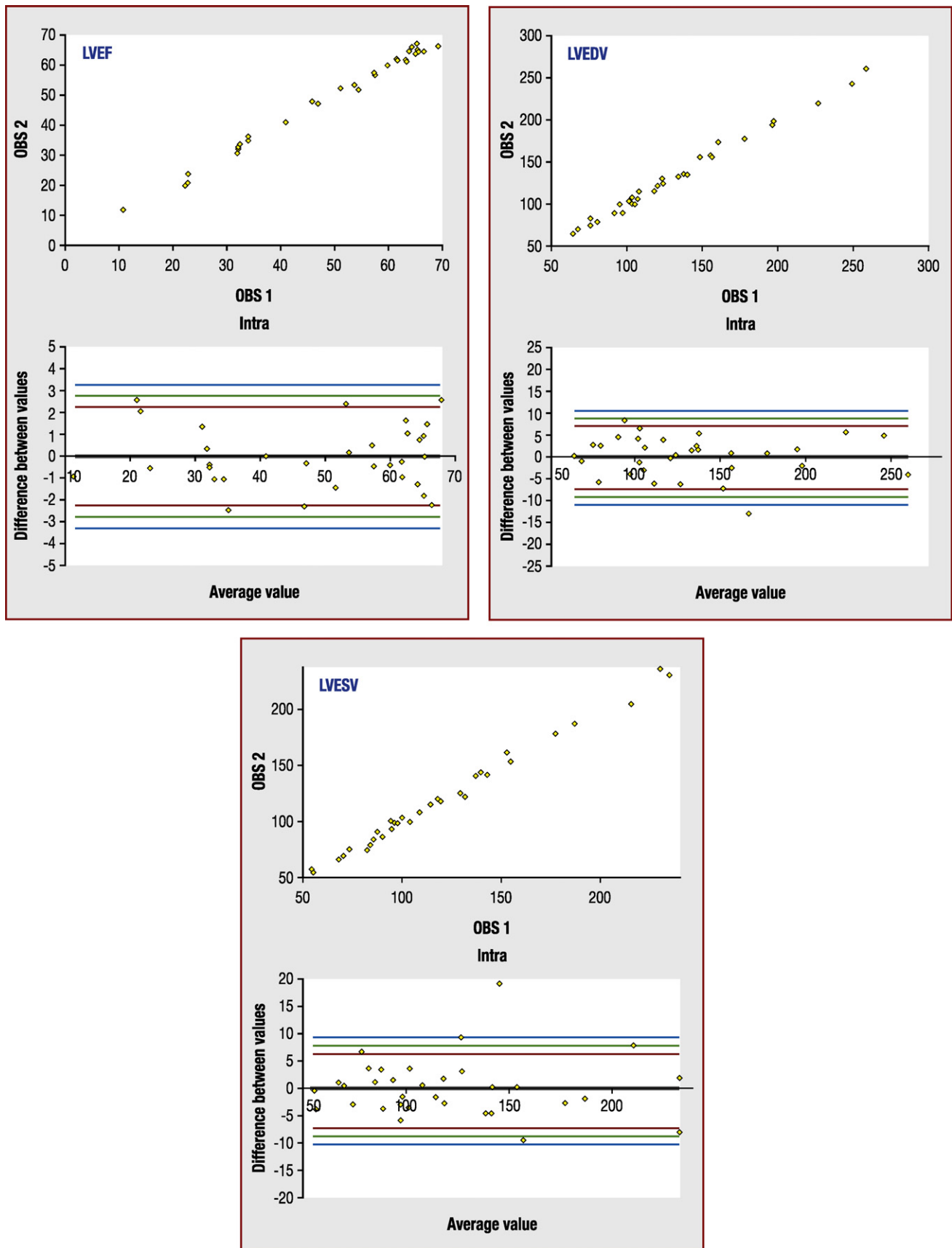
Characteristic	
Age (years)	$67.5 \pm 8$
Men	38 (86)
Ischaemic dilated cardiomyopathy	26 (59)
Non-ischaemic dilated cardiomyopathy	18 (41)
New York Heart Association class	$3.2 \pm 0.3$
Ejection fraction (%)	$25.8 \pm 7$
QRS width (ms)	$160 \pm 27$
Concomitant therapy	
ACE inhibitor	30 (68)
AT <sub>1</sub> receptor antagonist	10 (22)
Beta-blocker	40 (91)
Diuretic	44 (100)
Aldosterone antagonist	33 (75)

Values are mean  $\pm$  standard deviation or number (%).  
ACE: angiotensin-converting enzyme; AT<sub>1</sub>: angiotensin type 1.





**Figure 2.** Interobserver reproducibility in terms of three-dimensional left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV).



**Figure 3.** Intraobserver reproducibility in terms of three-dimensional left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV).

**Table 2** Demographic, clinical and echocardiographic characteristics at baseline in patients with left ventricular lead position concordant or non-concordant with most delayed site.

Characteristic	Group 1 (n = 19)	Group 2 (n = 25)	Group 1 vs 2 p	Group 3 (n = 21)	Group 4 (n = 23)	Group 3 vs 4 p
Age (years)	66.4 ± 6.5	68.5 ± 7.4	0.24	65.1 ± 6.3	69.9 ± 7.8	0.31
Men	16 (84)	22 (88)	0.72	17 (81)	21 (91)	0.32
Ischaemic heart disease	11 (58)	15 (60)	0.89	12 (57)	17 (74)	0.24
QRS duration (ms)	165 ± 21	157 ± 23	0.58	169 ± 20	153 ± 25	0.45
New York Heart Association functional class	3.2 ± 0.6	3.2 ± 0.6	0.88	3.1 ± 0.6	3.2 ± 0.6	0.81
QOL score	50 ± 17	57 ± 19	0.34	52 ± 14	56 ± 20	0.36
6-minute walking test (m)	302 ± 65	289 ± 72	0.43	292 ± 65	297 ± 72	0.48
Peak oxygen consumption (mL/kg/min)	13.6 ± 3.2	13.1 ± 3.6	0.54	12.9 ± 3.1	13.7 ± 3.6	0.39
LVESV (mL)	123 ± 56	133 ± 75	0.41	132 ± 69	126 ± 71	0.52
LVEDV (mL)	165 ± 65	180 ± 86	0.37	180 ± 84	166 ± 78	0.33
LVEF (%)	25.5 ± 7	26.1 ± 7	0.61	27 ± 7	24.7 ± 7	0.28
3D dyssynchrony index (%)	10 ± 2.8	9.8 ± 2.9	0.65	10.7 ± 2.8	9.2 ± 2.8	0.26

Values are mean ± standard deviation or number (%).  
QOL: quality of life.

## Discussion

### Impact of the left ventricular pacing site

In patients requiring CRT, the choice of optimal LV pacing site remains an issue. Systematic implantation of the LV

lead at the lateral wall is often recommended, simplifying the choice when a suitable lateral vein can be cannulated. However, the existence of an identical, unique, optimal pacing site, i.e., the lateral wall, for all implanted patients, despite major interpatient differences in electromechanical activation, seems very unlikely. Tailoring of the LV lead posi-

**Table 3** Percentage change between baseline and 6-month follow-up results in patients with LV lead position concordant or non-concordant with most delayed site.

	Group 1 (n = 19)	Group 2 (n = 25)	Group 1 vs 2 p	Group 3 (n = 21)	Group 4 (n = 23)	Group 3 vs 4 p
Δ New York Heart Association functional class (%)	-31 ± 11	-28 ± 13	0.27	-29 ± 10	-30 ± 14	0.35
Δ Minnesota QOL score (%)	-46 ± 26	-44 ± 21	0.45	-41 ± 22	-48 ± 25	0.28
Δ 6-minute walking test (%)	+42 ± 18	+38 ± 18	0.39	+39 ± 16	+42 ± 21	0.35
Δ Peak oxygen consumption VO <sub>2</sub> max (%)	+14 ± 5	+13 ± 6	0.17	+16 ± 6	+12 ± 4	0.27
Δ LVESV (%)	-21 ± 8	-24 ± 13	0.32	-24 ± 8	-23 ± 13	0.42
Δ LVEDV (%)	-15 ± 8	-18 ± 11	0.34	-18 ± 9	-16 ± 11	0.38
Δ LVEF (%)	+21 ± 14	+27 ± 15	0.18	+20 ± 12	+28 ± 17	0.14
Δ 3D dyssynchrony index (%)	-47 ± 22	-44 ± 24	0.34	-51 ± 19	-42 ± 26	0.17

Values are mean ± standard deviation.  
QOL: quality of life.

tion may provide additional haemodynamic improvement and optimization of the pacing site for each patient may be recommended. Therefore, any technique or strategy that might optimize LV lead position deserves interest.

## Echocardiography to select the optimal pacing site

In an experimental study that included a very limited number of patients, tailoring of the LV lead position to the area of maximal electrical delay resulted in the best acute resynchronization effect [16]. The human results in terms of clinical impact, reverse remodelling and reduction of mortality associated with this strategy are still controversial [17,18].

In our present study, echocardiographic optimization of the LV lead position based on a detailed analysis of the myocardial contraction sequence before implantation was not associated with additional short-term or long-term improvement. Our results contradict some results published previously, despite having a similar study design [11]. This discordance highlights the disparity in results obtained with echocardiography in the context of CRT. Our study (and others) combined complex techniques, such as tissue Doppler imaging, tissue synchronization imaging or real-time 3D echocardiography, to define the segment with most delayed activation. In a recent, prospective, multicentre trial, the ability of several conventional two-dimensional echocardiographic variables and techniques to predict response to CRT was evaluated [19]. Poor interobserver reproducibility with the use of these variables and techniques may explain why studies with similar design produce conflicting results. However, the absence of an additional beneficial effect with LV implantation in the most delayed region in our study might have a more pathophysiological explanation. In a high proportion of patients, biventricular pacing is performed with complete capture and absence of fusion between intrinsic and ectopic rhythms. Therefore, the electromechanical activation after CRT depends on the location of the pacing leads and on the electromechanical properties of the LV myocardium, independent of the LV activation pattern before implantation. As ventricular pacing induces areas of early activation around the pacing lead and areas of late activation at a distance from the lead, it is likely that stimulation in the most delayed region, determined in spontaneous rhythm, will convert this zone into an early activated site, whereas previous regions of early activation will be delayed. We believe that there is no reason for these modifications in electromechanical activation to be associated with a maximal reduction in ventricular dyssynchrony or with optimal acute haemodynamic or long-term clinical improvements. Furthermore, in patients with ischaemic cardiomyopathy, the most delayed segments are often composed of viable but ischaemic tissue, while pacing the ischaemic area has been demonstrated to be ineffective, if not deleterious [20]. Preprocedural echocardiography may not therefore be the adequate tool for predicting the optimal pacing sites.

In contrast, periprocedural echocardiographic comparisons between the different pacing sites may be technically difficult but more appropriate for determining the LV pac-

ing site, associated with maximal reduction in ventricular dyssynchrony and maximal haemodynamic improvement. Echocardiography may be performed during the procedure to determine the optimal LV pacing site based on a detailed analysis of the myocardial contraction sequence once the correct ventricular lead has been implanted. Our present study assessed the putative favourable impact of targeting the most delayed LV region during right ventricular pacing. Unfortunately, we did not demonstrate an increased benefit with an echocardiographically-optimized LV lead position targeting the exact region of maximal mechanical delay during right ventricular pacing. Therefore, just like preprocedural echocardiography, this strategy may not be helpful in improving the response to the therapy.

## Limitations

The study population size was rather small and the statistical analysis may have been underpowered. Moreover, the duration of follow-up was rather short. Therefore, this study should probably be considered as a pilot study. A multicentre, randomized study is warranted to confirm the clinical impact of pre-implantation echocardiographically guided selection of the LV pacing site.

## Conclusions

This prospective study compared the outcome of patients paced at the most delayed LV region with that of patients paced at any other LV site. Implantation of the LV lead in the most delayed region of the left ventricle determined by 3D echocardiography did not result in additional improvement in symptoms or LV function.

## Conflict of interest

None.

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